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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,626	01/10/2005	Manuel Rosa-Calatrava	017753-200	9366

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,626	ROSA-CALATRAVA ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,16,19-27,29-34,40 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 16, 19-27, 29-34, 40, and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/31/2008 has been entered.

Claims 2 and 5-7 have been cancelled. Claims 3, 4, 8-15, 17, 18, 28, 35-39, 42, and 43 have been withdrawn. Claim 1 has been amended.

Claims 1, 16, 19-27, 29-34, 40, and 41 are under examination.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 16, 19-27, 29-34, 40, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wickham et al. (U.S. Patent No. 6,455,314, of record), in view of both Wallach et al. (WO 97/37016, of record) and Seth et al. (U.S. Patent No 5,928,944, of record).

Wickham et al. teach **(i)** a mutated adenoviral fiber protein, wherein the adenoviral fiber protein comprises at least one mutation affecting the lysine at position 506, the histidine at position 508, and the serine at position 555 of the wild type adenoviral fiber protein set forth by SEQ ID NO: 1, and wherein the affected amino acid residues are involved in the interaction with cellular receptors containing glycosaminoglycans or sialic acid (claim 1), **(ii)** a trimer comprising the mutated adenoviral fiber protein (claim 16), **(iii)** a DNA encoding the mutated adenoviral fiber protein (claim 19), and **(iv)** an adenoviral particle wherein wild type adenoviral fiber is replaced with the mutated adenoviral fiber trimer above, wherein the adenoviral particle comprises a penton base having mutations affecting a native RGD sequence, wherein the adenoviral particle exhibits reduced ability to interact with the native receptors, wherein the adenoviral particle can further include non-native ligands that can bind cellular receptors and wherein the non-native ligands can be incorporated into the fiber at any location that exposes the ligand, such as the terminus of the fiber protein (i.e., genetically coupled to a viral polypeptide exposes at the surface, wherein one of the locations could be the C-terminus) (claims 20-27) (Abstract, column 7, lines 10-18 and 37-67, column 9, lines 20-67, column 10, lines 1-67, column 12, lines 29-31, column 17, lines 20-27, Table 1; see also the sequence alignment made of record in the final Office action of 12/31/2007). Wickham et al. teach that the adenoviral particle can comprise adenoviral genome and it can be replication defective (claims 30 and 31), that the adenoviral particle can be used deliver genes to target cells, wherein the genes are operably linked to tissue-specific promoters and wherein the target cells have surface

receptors capable of binding the ligand exposed on the surface of the adenoviral particle (claims 32-34) (column 13, lines 7-67, column 14, lines 25-30). Wickham et al. also teach a composition comprising the adenoviral particle and a pharmaceutically acceptable carrier (claim 40), wherein the adenoviral particle is conjugated to lipid derivatives of PEG (claim 41) (column 1, lines 42-50, column 14 bridging column 15).

Although Wickham et al. teach mutations affecting the lysine at position 506, the histidine at position 508, and the serine at position 555 of the wild type adenoviral fiber protein set forth by SEQ ID NO: 1, they do not specifically teach substituting the lysine in the position 506 by glutamine, the histidine in position 508 by lysine, or the serine in position 555 by lysine (claim 1). However, the prior art teaches obtaining protein analogs by using conservative substitutions such as replacing lysine with glutamine or histidine with lysine (see for example, Wallach et al. teach, p. 23, Table I A, p. 24, Table I B). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the adenoviral fiber protein at one the positions taught by Wickham et al., by using the conservative mutations taught by Wallach et al., with a reasonable expectation of success. It is noted that, by doing such, one of skill in the art would have obtained a modified fiber proteins having glutamine at position 506 or lysine at position 508 (claim 1). One of skill in the art would have been motivated to use such conservative mutations in order to obtain the desired binding activity, without altering the biological activity characteristic of an adenoviral fiber protein. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because Wallach et al. teach that only routine experimentation is required to determine

which substitution(s) results in the desired property (p. 22, lines 7-13). With respect to the limitation of the modified fiber having an affinity for its receptor of at least one order of magnitude less than the wild type (claim 1), the mutated adenoviral fiber of Wickham et al. and Wallach et al. must necessarily exhibit this property because it is obtained by substituting lysine in the position 506 with glutamine, the histidine in position 508 with lysine, and the serine in position 555 with lysine.

Wickham et al. and Wallach et al. do not teach the adenoviral particle being an empty capsid (claim 29). Seth et al. teach a method of adenoviral-mediated transfection, wherein the adenovirus is an empty capsid (Abstract, column 5, lines 22-35, column 8, lines 54-58). It would have been obvious to one of skill in the art, at the time the invention was made, to obtain an empty adenovial capsid comprising the mutated fiber protein of Wickham et al. and Wallach et al., with a reasonable expectation of success. One of skill in the art would have been motivated to obtain such capsids to use them according to the teachings of Seth et al., who disclose that such capsids are efficient in mediating transfection without destroying the host cell (column 8, lines 24-58). One of skill in the art would have been expected to have a reasonable expectation of success in making empty capsid because the art teaches that such capsids can be successfully obtained.

Thus, the claimed invention was *prima facie* obvious at the time the invention

Applicant argues that was made the mere fact that the prior art can be modified does not make such a modification obvious unless the prior art or some other evidence

suggests the desirability of the modification. Here, no such factors or motivation for combining Wickham, Wallach and Seth exist. In particular, Applicant argues, one of ordinary skill in the art would not have been led to modify the adenoviral fiber proteins of Wickham to include the specific substitutions (i.e., lysine in position 506 with glutamine, histidine in position 508 with lysine, or serine in position 555 with lysine), defined in independent Claim 1, based on the disclosures of Wallach or Seth. In fact, Applicant submits that Wickham actually teach avoid making substitutions at positions 506, 508 and 555. For example, Wickham describes adenoviral fiber mutants impaired in binding to the primary CAR receptor, wherein a series of fiber mutants were constructed, three of which encompass modifications in positions 506, 508 and 555 (the A K (506) having the Lys residue in position 506 deleted, the H(506)A mutant having the substitution of the His residue in position 506 (which should be 508) by an Ala residue, and the S(551) N+S (555) N mutant with substitutions of the Ser residues in position 551 and 555 by Asp residues, respectively. (See, Wickham at Table 1, col. 18.) However, when tested for CAR binding, none of the fiber mutants demonstrated reduced affinity for that receptor. Thus, these fiber mutants are not listed in Table 2. Wallach relates to TRAF binding proteins and, more specifically, analogs of TRAF binding proteins that exhibit "conservative" changes, which are not expected to change the size, charge, configuration or biological activity of the protein. (See, Wallach at page 22, lines 3-6.) In this regard, Wallach provides two lists of possible conservative substitutions. (See, Wallach at Tables 1A and 1 B). Seth describes an adenovirus-mediated method of plasmid transfection through a co-internalization process. Gene expression is

significantly increased when plasmid transfection is performed in the presence of adenovirus or empty capsids (see, Seth at Example 10, col. 25 to 26), especially when bound to the cellular receptor. (See, Seth at Example 5, col. 19.) Thus, Wickham discloses that modifying adenoviral fibers in the distal part of the fiber protein at positions downstream of residue 492 has no effect on receptor binding. (See, Table 2 of Wickham where mutations reducing CAR binding are located in positions 408-409, 412-417, 420, 474-477, 487, and 492). Accordingly, Wickham would lead one of ordinary skill to expect that residues in positions 506, 508 and 555 are not available for interaction with the cellular receptors and would not motivate one of ordinary skill to introduce amino acid substitutions at these positions when attempting to impair binding of the fiber to cellular HGS receptors. Indeed, Wickham actually teaches away from making the asserted combination to arrive at the claimed invention. Wallach does not overcome the deficiencies of Wickham. In particular, Wallach discloses protein analogs that can be generated by introducing conservative substitutions. However, it is important to note the fact that the described conservative substitutions are intended to preserve biological activity of protein analogs (i.e., maintain biological and structural properties of the polypeptide after amino acid substitutions). (See, Wallach at page 22, lines 3-6 and page 24, lines 26-28.) In stark contrast, the amino acid substitutions defined in Claim 1 modify the fiber protein's biological activity (e.g., its ability to bind with cellular HGS receptors). Therefore, one of ordinary skill seeking to impair adenoviral fiber interaction with cellular receptors would not have looked to the conservative substitutions of Wallach because Wallach states that the conservative substitutions are intended to

preserve (not change) the protein's biological activity (e.g., impairment of receptor binding). Seth also fails to overcome the deficiencies of Wickham. Indeed, Seth fails to disclose or fairly suggest how adenovirus fibers interact with cellular receptors, which amino acid residues are involved in the interaction, or how one should, or even could, modify adenovirus fiber proteins to impair receptor binding. Applicant submits that the Office Action has not demonstrated that one of ordinary skill in the art would have combined the cited references. Thus, Applicant contends that there is no basis, absent the impermissible use of hindsight based on Applicants' disclosure, for combining the references, as suggested in the Official Action. The only motivation for making the claimed modifications comes from the present specification, which teaches the desirability of the claimed combination of features to obtain reduced affinity for glycosaminoglycan and/or sialic acid-containing cellular receptors. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA

1971). It is noted that the instant claims are drawn to a composition which is taught by the combination of references above. Specifically, Wickham et al. teach that the substitutions of lysine at position 506, the histidine at position 508, and serine at position 555 in the wild type adenoviral fiber are among the preferred mutations (column 7, lines 10-18, Table 1). Such a disclosure of "preferred" mutations certainly is not a teaching away from the claimed invention. Applicant argues that, when tested for CAR binding, none of the three fiber mutants encompassing modifications in positions 506, 508 and 555 demonstrated reduced affinity for that receptor. However, there is no such teaching in Wickham et al. Just because the above substitutions are not included in Table 2 does not mean that Wickham et al. teach against them. This is evidenced by the fact that that Wickham et al. claim these mutations (see claim 2 in Wickham et al.). The fact is that Wickham et al. teach a composition comprising an adenoviral fiber protein mutated at positions 506, 508 and 555, as claimed. With respect to Wallach et al., Applicant argues that the reference relates "conservative" changes, which are not expected to change the size, charge, configuration or biological activity of the protein. (See, Wallach at page 22, lines 3-6). However, the cited passage does not refer to the conservative substitution disclosed in Table 1A; Wallachet al. teach that the conservative substitutions presented in Table IA result in modified structural and functional properties of a polypeptide molecule while maintaining the biological activity (p. 22, lines 7-13). One of skill in the art would understand that, in the instant case, modifying binding to adenoviral cell surface receptors (i.e., function) would mean modifying fiber structure (it is a well-known fact in the art that receptor binding, i.e.,

function, is dependent on structure). Since it is known that the adenoviral fiber is necessary for viral replication (see Von Seggern et al., J Virol., 1999, 73: 1601-1608, Abstract, p. 1601, column 2, p. 1602, column 2), maintaining biological activity would mean maintaining its role in virus propagation. Therefore, one of skill in the art seeking to retarget adenoviral vectors would use the mutations of Wickham et al. and Wallach et al. to abolish fiber binding to the native receptors, while maintaining its ability to promote viral propagation. Seth et al. was cited for teaching other claim limitations, and not the instant substitutions. The rejection is maintained.

Conclusion

4. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Von Seggern et al. (J Virol., 1999, 73: 1601-1608) was cited in response to Applicant's argument that one of ordinary skill seeking to impair adenoviral fiber interaction with cellular receptors would not have looked to the conservative substitutions of Wallach because Wallach states that the conservative substitutions are intended to preserve the protein's biological activity (in the instant case, according to Applicant, this would mean to preserve receptor binding). Von Seggern et al. teach that the fiber protein is essential for viral replication. Based on the teachings in the art as a whole, one of skill in the art seeking to change fiber affinity for its receptors would understand that preserving biological activity means preserving the essential role of the fiber protein in viral replication.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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